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Scientific Article

Patterns of Failure After Adjuvant Stereotactic Body Radiation Therapy for Pancreatic Cancer With Close or Positive Margins

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Abstract

Purpose: There is no consensus on treatment volumes for adjuvant stereotactic body radiation therapy (SBRT) for pancreatic cancer. Herein, we report patterns of failure after pancreatic SBRT for close/positive margins, which may inform target volume design.

Methods and Materials: An institutional review board-approved retrospective review of patients with pancreatic adenocarcinoma treated with adjuvant SBRT for close/positive margins from 2009 to 2018 was conducted. Patterns of failure were defined as local (LF) within the tumor bed, regional (RF) within lymph nodes or anastomoses, or distant (DF). The cumulative incidence of locoregional failure was calculated using the cumulative incidence function accounting for the competing risk of death. LFs were mapped to the planning target volume (PTV) and classified as in-field (completely within the PTV), marginal (partially within the PTV), or out-of-field (completely outside the PTV). The location of LFs was compared with the Radiation Therapy Oncology Group 0848 contouring atlas to determine whether standard postoperative radiation therapy volumes would have included the LF.

Results: Seventy-six patients were treated with adjuvant SBRT for close (51.3%) or positive (48.7%) margins. Most (81.6%) received 36 Gy in 3 fractions, with a median PTV volume of 17.8 cc (interquartile range, 12.1-25.6). With a median follow-up of 17.0 months (interquartile range, 7.3-28.4), crude rates of first isolated LF, isolated RF, and DF +/− LF or RF were 9.2%, 6.6%, and 56.6%, respectively. Two-year cumulative incidences of LF, RF, locoregional failure, and DF were 34.9%, 30.8%, 49.2%, and 60.4%, respectively. Of 28 reviewable LFs, 21.4% were in-field while the remainder were completely outside (60.7%) or partially outside (17.9%) the PTV. Most LFs (92.9%) would have been encompassed by the Radiation Therapy Oncology Group consensus target volumes.

Conclusions: After adjuvant pancreatic SBRT for close/positive margins, the majority of LFs were outside the PTV but within contemporary target volumes for conventional radiation therapy.

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Introduction

Pancreatic cancer is a highly lethal malignancy, responsible for the fourth-highest cancer death rate in the United States. Despite advances in management, 5-year overall survival (OS) remains dismal at 9%.[1] Resection remains the most important curative modality; however, 80% to 85% of patients are unresectable at presentation.[2,3] Of resectable patients, 20% to 30% have positive margins (R1) and fare worse than patients with negative margins (R0), even with adjuvant chemotherapy.[4-12] Adjuvant radiation therapy (RT) may thus have a role after R1 resection and for other high-risk patients; however, studies examining adjuvant RT have produced conflicting results.[9,12-20] The role of adjuvant RT is currently being examined in Radiation Therapy Oncology Group (RTOG) 0848.[21]

One concern with adjuvant conventionally fractionated RT is the delay to initiating systemic chemotherapy, owing to time needed to deliver RT over 5 to 6 weeks as well as potential interruptions in treatment from treatment-induced toxicities. Micrometastatic spread before adjuvant chemotherapy may offset any locoregional control benefits with adjuvant RT. For these reasons, adjuvant stereotactic body radiation therapy (SBRT) delivered over a few fractions may be an attractive option for select patients. Definitive pancreatic SBRT provides local control rates of 70% to 80%.[22-24] Adjuvant pancreatic SBRT provides similar local control with mild toxicities, though the body of evidence for adjuvant SBRT is limited.[25-27] A previous report of a prospective trial from our institution involving 50 patients who received adjuvant pancreatic SBRT for close/positive margins showed 2-year local and regional control of 77% and 73%, respectively. Acute grade 3+ toxicity was 4.1%, and no late grade 3+ toxicity or changes in patient-reported quality of life were evident.[25]

Although SBRT may provide some advantages over conventionally fractionated RT, 1 disadvantage to SBRT is the size limit on treatment volumes. Dose constraints of adjacent organs, chiefly the duodenum, limit the ability to dose-escalate in this region. Thus, SBRT target volumes are often limited to areas of highest risk of recurrence (ie, the positive margin or critical vascular interfaces); coverage of regional lymph nodes (LNs) and other areas at risk for harboring microscopic disease are usually omitted. Furthermore, although guidelines exist to standardize treatment volumes with adjuvant conventionally fractionated RT, no such consensus has been reached for pancreatic SBRT volumes. Contouring guidelines for postoperative conventionally fractionated RT were developed based on studies examining patterns of failure (POF), and recommend inclusion of surgical anastomoses and regional LNs (Table 1).[28] Limited treatment volumes with SBRT that omit areas adjacent to the tumor or tumor bed may not be adequate in preventing adjacent local or regional recurrences.

Few studies have reported POF after pancreatic SBRT to inform appropriate treatment volumes.[29,30] No studies, to our knowledge, have examined failure locations relative to treatment volumes after adjuvant pancreatic SBRT. Herein we report POF in patients treated with adjuvant pancreatic SBRT for close/positive margins.

Methods and Materials

Eligibility

An institutional review board-approved retrospective review of consecutive patients treated between October 2009-February 2018 with adjuvant pancreatic SBRT for close/positive margins was conducted. During this time, many patients were treated in a prospective observational trial at our institution , results of which have been previously reported.[25] Patients in this trial were included in this retrospective review if they met inclusion criteria. Demographic, clinical, pathologic, and treatment details were collected. Included patients had resectable or borderline resectable pancreatic adenocarcinoma and were treated with resection and adjuvant pancreatic SBRT for close/positive margins. Resectability definitions were based on National Comprehensive Cancer Network guidelines available at the time of treatment. Generally, resectable patients had no arterial tumor contact and/or $\leq 180^\circ$ venous tumor contact without vein contour irregularity, while borderline resectable patients had arterial tumor contact $\leq 180^\circ$ and/or venous tumor contact $>180^\circ$ or $\leq 180^\circ$ with contour irregularity that was amenable to vein reconstruction. Patients underwent pancreaticoduodenectomy or distal pancreatectomies for pancreatic tail tumors $\pm$ robotic assistance. Positive surgical margins included viable tumor cells present at any resection margin. Close margins included viable tumor cells present within 2 mm of any resection margin. Patients received adjuvant or neoadjuvant chemotherapy or both per physician discretion and patient tolerance. Experimental systemic therapy was allowed in institutional protocols based on eligibility and patient/physician preference.

Stereotactic body radiation therapy

Patients were simulated supine with arms raised and vacuum lock bag immobilization. Axial computed tomography (CT) images with 1.25 mm slice thickness were obtained. Intravenous and/or enteral contrast was administered per physician discretion. Four-dimensional CT data were acquired to evaluate target motion. The clinical target volume (CTV) was delineated in

conjunction with the operating surgeon and included the area of close/positive margin, clips/fiducials, and other areas at high risk of microscopic disease based on the pathology report. Abutting vasculature was only included if that specific vessel margin was close/positive and was otherwise not routinely included. Elective regional LNs were not included in the CTV. The planning target volume (PTV) included margins for set-up error and target motion and was altered accordingly to respect critical structure tolerance. All patients were treated with 3 fractions of SBRT, every other day, to a dose of 27 to 36 Gy using daily cone beam CT for image guidance. Patients were typically seen 10 to 12 weeks post-SBRT, then every 3 months for 1 year, with subsequent follow-up per physician discretion. CT scans were typically obtained at each follow-up or if there was a concern for recurrence or progression.

Endpoints and statistical analysis

Clinical notes and radiologic images/reports were reviewed to capture recurrences. For patterns of failure analysis, failures were classified as local (LF), regional (RF), locoregional (LRF), or distant (DF) as deemed by the reading radiologist and/or treating physician in radiology reports and/or clinical notes. LFs were recurrences within the operative bed. RFs were recurrences within the regional LNs (new or enlarging LNs) or anastomosis. LRFs were defined as local and/or regional failures. DFs were recurrences in nonregional LNs or distant organs. The date of recurrence was backdated to the initial imaging study demonstrating any radiographic evidence of progression. Both the site of first failure and the cumulative incidence of all failure types were collected. All patients were evaluated for LF and RF from SBRT completion to death or loss of follow-up, regardless of progression at other sites.

SBRT treatment plans were accessed to map LFs relative to the PTV. In-field LFs were LFs completely within the PTV. Marginal failures were LFs partially within the PTV, and out-of-field were LFs completely outside the PTV. The location of LFs and RFs was compared with the RTOG 0848 consensus volumes for postoperative treatment of pancreatic cancer[28] to determine whether consensus volumes for conventionally fractionated postoperative RT would have included the LF or RF. Recommended contours of each region of interest and CTV expansions were considered when determining whether an LF/RF would have been encompassed by the RTOG consensus volumes (Table 1). To successfully map LFs and RFs relative to the PTV and the RTOG consensus volumes, the location of each failure relative to the preoperative tumor location and measured distances between the edge of failures and prominent abdominal anatomy (eg, celiac artery [CA], superior mesenteric artery [SMA], portal vein, anastomoses) were recorded and compared with the location and measured distances of the PTV volumes and RTOG consensus volumes relative to the same anatomic landmarks. Patients without available SBRT plans or imaging evidence of LF/RF were excluded from analysis of failure location.

Crude failure rates were calculated from the number of each failure type within the cohort. Time-to-event analysis was calculated from the date of SBRT completion to the date of the event. OS was calculated using Kaplan-Meier methods. The cumulative incidence function was used to calculate the cumulative incidence of LF, in-field LF, marginal LF, out-of-field LF, RF, LRF, and DF +/− LF or RF from the last day of SBRT treatment to the date of failure, accounting for the competing risk of death.[31-33] Differences in time to LF by type of LF were analyzed with the log-rank test. Cox proportional hazards regression was used to test the effect of demographic, clinical, pathologic, and SBRT treatment details on the risk of LF and in-field LF. Log-minus-log plots were used to confirm the proportional hazards assumption. As a sensitivity analysis, continuous variables were also tested as binary categorical variables stratified by the median value. Variables with P values $< .10$ on univariate analysis were entered into the multivariate model, which was run with backward stepwise selection. P values $< .05$ were considered statistically significant. Statistical analysis was conducted with Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 25.0 (SPSS Inc, Chicago, IL) and R version 3.6.2.[34]

Results

Seventy-six patients were treated with adjuvant SBRT for close/positive margins. Table 2 outlines cohort characteristics. Most patients (56.6%) were male and had pancreatic head tumors (80.3%). Most (59.2%) received neoadjuvant chemotherapy, most commonly gemcitabine/nab-paclitaxel (48.9%). The majority (81.6%) received adjuvant chemotherapy, most commonly gemcitabine (41.9%).

Three-quarters of patients were resectable and 25.0% were borderline resectable. Most patients (86.8%) underwent pancreaticoduodenectomy. Close margins were seen in 51.3%; positive margins were seen in 48.7%. The most common positive/close margin was retroperitoneal (52.6%). Twenty patients (26.3%) had multiple positive/close margins. More than 3/4 (77.6%) had pathologic T2 disease. Pathologic nodal staging was variable: pN0, pN1, and pN2 was seen in 26.3%, 39.5%, and 34.2%, respectively.

Adjuvant SBRT was delivered a median 2.2 months after surgery (interquartile range [IQR], 1.7-3.0). Most patients (81.6%) received 36 Gy in 3 fractions. Median PTV was 17.8 cc (IQR, 12.1-25.6). Median equivalent

Table 1 Radiation Therapy Oncology Group consensus treatment volumes for conventionally fractionated postoperative pancreatic radiation therapy.[28]

Region of interest	RTOG* recommendations for volume delineation	Expansions for CTV
Postoperative bed	Based on preoperative tumor location and pathology reports; include surgical clips.	±0.5-1.0 cm
Anastomoses	Pancreaticojejunostomy (PJ), choledochaljejunostomy, or hepaticojejunostomy. Do not include pancreaticogastrostomy if present.	0.5-1.0 cm
Abdominal nodal regions		
Celiac artery (CA)	Most proximal 1.0-1.5 cm	1.0-1.5 cm
Superior mesenteric artery (SMA)	Most proximal 2.5-3.0 cm (includes peripancreatic nodes)	1.0-1.5 cm
Porta hepatic	Portal vein (PV) segment that runs anterior and anteromedial to the inferior vena cava.	1.0-1.5 cm
Para-aortic	Aorta from most cephalad aspect of CA, PJ, or PV (whichever is most cephalad), to bottom of L2; cover to bottom of L3 if needed to encompass extent of preoperative tumor.	2.5-3.0 cm to the right, 1.0 cm to the left, 2.0-2.5 cm anteriorly, and 0.2 cm posteriorly toward the anterior edge of the vertebral body.

Abbreviations: CTV = clinical target volume; RTOG = Radiation Therapy Oncology Group (RTOG).

dose in 2-Gray-per-fraction using alpha:beta = 10 and biologically effective dose using alpha:beta = 10 was 66.0 Gy (IQR, 66.0-66.0) and 79.2 Gy (IQR, 79.2-79.2), respectively. No patient had a significant interruption during SBRT; the median time elapsed during the SBRT course was 6.0 days (IQR, 5.0-7.0).

Median follow-up after SBRT completion was 17.0 months (IQR, 7.3-28.4). Median OS was 17.3 months (95% confidence interval, 11.0-23.5 months). Fifty-seven patients (75.0%) experienced a recurrence at any site during follow-up. Table 3 outlines POF. Upon examination of sites of first failure, isolated DF was predominant (30.2%, n = 23). LF was a component of first failure in 23 patients. Crude rates of isolated LF, isolated RF, and DF +/− LF or RF at first failure were 9.2%, 6.6%, and 56.6%, respectively. A total of 32 (42.1%), 24 (31.6%), 42 (55.3%), and 50 patients (65.8%) developed a LF, RF, LRF, or DF, respectively, during follow-up. Upon examination of LF or RF, 18 patients (23.7%) had an LF ± DF but without RF, 10 patients (13.2%) had an RF ± DF but without LF, and 14 patients (18.4%) had both LF and RF ± DF. The 2-year cumulative incidence of LF, RF, LRF, or DF, accounting for the competing risk of death, was 34.9%, 30.8%, 49.2%, and 60.4%, respectively (Fig 1). Univariate Cox regression did not reveal any statistically significant predictors of LF (Table 4), although a trend was seen for positive pancreatic neck margin ($P = .056$).

Of 32 patients with an LF during follow-up, 3 patients had unavailable imaging of the LF, and 1 patient had an unavailable SBRT plan. Thus, 28 of 32 patients (87.5%) were analyzed for POF relative to treatment volumes. Only 21.4% (n = 6) of LFs were in-field; the remaining were out-of-field (60.7%, n = 17) or marginal (17.9%, n = 5). The 2-year cumulative incidence of in-field, marginal, and out-of-field LFs was 7.3%, 5.8%, and 17.9%, respectively. There were no differences in time to LF based on type of LF; median time to failure for in-field, marginal, and out-of-field LFs was 5.0, 8.0, and 11.8 months, respectively ($P = .477$). All 6 patients with an in-field LF received 36 Gy in 3 fractions and had larger CTV (median, 15.2 cc; IQR, 12.4-16.7) and PTV (median, 27.5 cc; IQR, 22.0-33.9) volumes relative to the entire cohort. However, no variables correlated with risk of in-field LF (Table 4).

Because RTOG consensus volumes cover areas at risk for LF and RF, every LF (n = 28) and RF (n = 24) with available imaging was examined to assess its location relative to recommended RTOG consensus volumes. Most LFs (92.9%, n = 26) would have been encompassed by the RTOG consensus volumes for postoperative conventional RT. Two LFs (7.1%) were deemed to be outside RTOG consensus volumes. Both were infiltrative masses that spread along and cuffed the distal SMA >5 cm beyond the SMA origination from the aorta, and thus outside the caudal extent of the recommended SMA target volume.

Upon examination of RFs, 62.5% (n = 15) would have been encompassed by RTOG consensus volumes. Of 9 RFs deemed to be outside RTOG consensus volumes, 5 were in high para-aortic or gastrohepatic LNs located ≥1 cm above the recommended cephalad border of the para-aortic LN target volume, 2 were in para-aortic LNs below the recommended caudal extent of the para-aortic LN volume, and 2 were in mesenteric LNs in the

Table 2 Demographic, clinical, pathologic, and treatment detail characteristics of cohort

Characteristic	Value (n = 76)
Age at diagnosis (median, IQR)	66.0 (57.3-73.0)
Sex (n, %)	
Male	43 (56.6)
Female	33 (43.4)
Tumor location (n, %)	
Body	8 (10.5)
Head	61 (80.3)
Tail	2 (2.6)
Uncinate process	4 (5.3)
Neck	1 (1.3)
Resectability (n, %)	
Resectable	57 (75.0)
Borderline resectable	19 (25.0)
Surgery type (n, %)	
Pancreaticoduodenectomy	66 (86.8)
Distal pancreatectomy	10 (13.2)
Margin status (n, %)	
Positive	37 (48.7)
Close (1 mm)	37 (48.7)
Close (2 mm)	2 (2.6)
Location of positive/close margin (n, %)	
Retroperitoneal	40 (52.6)
Vascular groove	35 (46.1)
Pancreatic neck	11 (14.5)
Chemotherapy (n, %)	
Neoadjuvant	45 (59.2)
Gemcitabine	2 (4.4)
FOLFIRINOX	6 (13.3)
Gemcitabine/nab-paclitaxel	22 (48.9)
Gemcitabine/hydroxychloroquine	9 (20.0)
Other	6 (13.3)
Adjuvant	62 (81.6)
Gemcitabine	26 (41.9)
FOLFIRINOX	4 (6.5)
Gemcitabine/capecitabine	10 (16.1)
Gemcitabine/nab-paclitaxel	13 (21.0)
FOLFOX	4 (6.5)
Other	5 (8.1)
Pathologic T stage (AJCC 8th edition) (n, %)	
pT1a	1 (1.3)
pT1c	6 (7.9)
pT2	59 (77.6)
pT3	10 (13.2)
Pathologic N stage (AJCC 8th edition) (n, %)	
pN0	20 (26.3)
pN1	30 (39.5)
pN2	26 (34.2)
SBRT regimen (n, %)	
36 Gy in 3 fractions	62 (81.6)
30 Gy in 3 fractions	13 (17.1)
27 Gy in 3 fractions	1 (1.3)
$EQD2_{10}$ (median, IQR)	66.0 (66.0-66.0)
BED_{10} (median, IQR)	79.2 (79.2-79.2)
CTV volume (median, IQR)	9.7 cc (6.8-14.4)
PTV volume (median, IQR)	17.8 cc (12.1-25.6)
PTV V100% (median, IQR)	94.8% (90.3-98.1)
Months from surgery to SBRT start (median, IQR)	2.2 (1.6-3.0)
Days elapsed from SBRT start to end (median, IQR)	6.0 (5.0-7.0)

(*continued on next page*)

Table 2 (*continued*)

Abbreviations: AJCC = American Joint Committee on Cancer; BED_{10} = biologically effective dose using an alpha/beta ratio of 10; CTV = clinical target volume; $EQD2_{10}$ = equivalent dose in 2 Gray per fraction using an alpha/beta ratio of 10; IQR = interquartile range; PTV = planning target volume; PTV V100% = percent of PTV that received 100% of the prescription dose; SBRT = stereotactic body radiation therapy.

anterior or lower abdomen along the distal SMA, beyond the recommended SMA nodal target volume. The 2-year cumulative incidence of LRF within RTOG consensus volumes was 39.3%.

Discussion

In this single-institution retrospective analysis of adjuvant pancreatic SBRT for close/positive margins, we identified a high rate of LRF outside the SBRT PTV but within contemporary RT target volumes. Although the predominant POF at first failure was isolated DF (30.2%), 42.1% of patients developed an LF during follow-up. The 2-year cumulative incidence of LF was 34.9%. Thus, despite macroscopic resection, targeted RT, and systemic therapy, patients with close/positive margins were at substantial risk for developing an LF. LFs within the PTV were infrequent (6 of 28 patients); the 2-year cumulative incidence of in-field LFs was 7.3%. Most LFs were completely outside the PTV (60.7%). Over 90% of LFs would have been encompassed by RTOG consensus volumes for postoperative conventionally fractionated RT for pancreatic cancer.

This study is the first, to our knowledge, that describes POF after adjuvant SBRT. Published studies examining POF with pancreatic SBRT are limited to patients treated in the definitive or neoadjuvant setting, and few studies have detailed examination of failures relative to treatment volumes or abdominal vasculature.[29,30,35] A Chinese study of >500 medically inoperable patients treated with pancreatic SBRT revealed that most LFs occurred near the CA, SMA, or splenic artery for pancreatic tail tumors[29]; 80% and 95% of failures near the CA or SMA occurred within 11 and 13 mm of the vessel, respectively. These failures likely would have been included within the consensus postoperative target volumes for conventionally fractionated RT. In-field failures (>80% of volume

Table 3 Patterns of failure with adjuvant SBRT

	Crude rates	Cumulative incidence (95% CI)		
	n (%)	6-month	12-month	24-month
Location of failure based on clinical documentation (n = 76)				
No failure	19 (25.0)			
Local failure	32 (42.1)	17.2% (9.7-26.5)	29.3% (19.5-39.8)	34.9% (24.3-45.8)
Regional failure	24 (31.6)	13.2% (6.7-21.2)	23.9% (15.0-34.0)	30.8% (20.7-41.5)
Locoregional	42 (55.3)	26.3% (17.0-36.6)	40.8% (29.7-51.5)	49.2% (37.4-59.9)
Distant failure	50 (65.8)	33.1% (22.7-43.4)	50.5% (38.7-61.2)	60.4% (48.2-70.5)
Location of local failure in patients with available plans and imaging (n = 28)				
In-field	6 (21.4)	4.2% (1.1-10.8)	5.7% (1.8-12.9)	7.3% (2.7-15.2)
Marginal	5 (17.9)	2.9% (0.1-8.9)	5.8% (1.9-13.2)	5.8% (1.9-13.2)
Out-of-field	17 (60.7)	8.0% (3.3-15.6)	14.8% (7.8-23.9)	17.9% (10.1-27.6)

Abbreviations: CI = confidence interval; SBRT = stereotactic body radiation therapy.

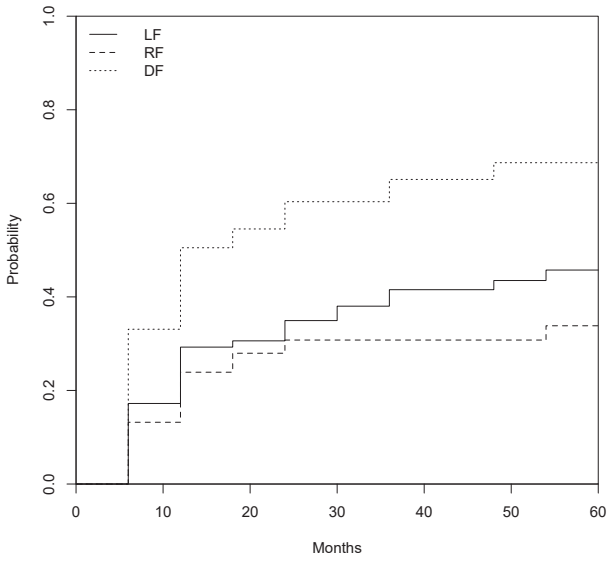

Figure 1 Cumulative incidence of local failure (LF), regional failure (RF), and distant failure (DF).

within the prescription isodose) occurred in 22.9%; this number mirrors the in-field failure rate in this study of 21.4%. The distance from primary tumors to retroperitoneal recurrences was larger than the distance from primary tumors to the CA (11.7 vs 9.0 mm, respectively), suggesting that asymmetrical expansion of SBRT target volumes to include the local retroperitoneal space may be warranted. Kharofa et al[30] reported POF in 18 resectable or borderline resectable patients treated with neoadjuvant pancreatic SBRT (33 Gy in 5 fractions) to the tumor and entire circumference of the abutting vessel. After interim analysis showed 2 of 8 patients failed locally at the vessel at the PTV margin, the remaining patients received 25 Gy in 5 fractions simultaneously to an additional PTV covering the entire pancreatic head/body, with extension of vessel coverage to the CA origin and SMA. With the limitations of a small sample size, the combined PTV approach led to longer 1-year PFS (60% vs 25%; $P = .03$), 2-year OS (67% vs 25%; $P = .03$), and lower 1-year cumulative incidence of LF (38% vs 70%; $P = .45$), raising the question of whether elective coverage of vessel origins with SBRT reduces the risk of failures at the margin of the primary PTV.

There are no consensus pancreatic SBRT volumes. Results from our study support consideration for expanding treatment volumes if feasible. Indeed, initial results from our institutional prospective trial of adjuvant pancreatic SBRT for close/positive margins found CTV volume was the only predictor for freedom from LF on multivariate analysis (hazard ratio, 1.095; 95% confidence interval, 1.005-1.193; $P = .038$).[25] However, the tradeoff between expanding target volumes and irradiating more normal tissue must be carefully evaluated. A study by Dholakia et al[36] generated hypothetical adjuvant intensity modulated radiation therapy and SBRT volumes encompassing the majority of LFs in >200 patients after pancreaticoduodenectomy. CTV volumes encompassed either 90% of LFs (CTV90) or 80% of LFs (CTV80) based on specific asymmetrical expansions around CA and SMA contours. With no further margins for setup error, PTV80 and PTV90 volumes ranged from 123.0 to 139.6 cc and 183.2 to 215.7 cc, respectively. These volumes are significantly larger than those in our study but may represent a practical strategy to expand treatment volumes while minimizing irradiation of normal tissue. Although the authors report critical structure dose constraints were met with 25 Gy in 5 fractions to the PTV90 with a simultaneous integrated boost to 33 Gy to PTV80, no patients were actually treated using the hypothetical plans.

The aforementioned studies highlight the commonality of LFs along vessels after SBRT and underline the importance of detailed POF examinations. Studies reporting LFs after pancreatic SBRT use different LF definitions, which may inadvertently include nodal failures — the Chinese and Dholakia studies defined LFs as

Table 4 Univariate Cox regression for predictors of LF in all patients (n = 76) as deemed by the reading radiologist and/or treating physicians and for predictors of in-field LF in patients with documented LF who had available plans and imaging (n = 28)

Univariate analysis				
Variable	HR for LF (95% CI)	*P* value	HR for in-field LF (95% CI)	*P* value
Age at diagnosis	1.00 (0.96-1.03)	.769	1.06 (0.96-1.17)	.259
Sex		.565		.441
Male	Reference		Reference	
Female	0.81 (0.40-1.66)		1.88 (0.38-9.42)	
Tumor location		.999		.650
Body	Reference		Reference	
Head	1.05 (0.36-3.04)		0.33 (0.06-1.81)	
Tail	1.44 (0.16-13.04)		NR	
Uncinate process	1.05 (0.19-5.80)		NR	
Neck	NR		NR	
Resectability		.127		.856
Resectable	Reference		Reference	
Borderline resectable	1.83 (0.84-3.96)		1.17 (0.21-6.60)	
Surgery type		.600		.501
Pancreaticoduodenectomy	Reference		Reference	
Distal pancreatectomy	1.27 (0.52-3.10)		1.79 (0.33-9.82)	
Margin status		.862		.395
Positive	Reference		Reference	
Close (1 mm)	0.87 (0.42-1.78)		0.87 (0.14-5.29)	
Close (2 mm)	0.62 (0.08-4.79)		4.26 (0.37-49.65)	
Retroperitoneal margin		.279		.465
Negative	Reference		Reference	
Positive/close	1.48 (0.73-3.03)		1.89 (0.34-10.51)	
Vascular groove margin		.256		.717
Negative	Reference		Reference	
Positive/close	0.66 (0.32-1.35)		0.73 (0.13-4.02)	
Pancreatic neck margin		.056		.847
Negative	Reference		Reference	
Positive/close	2.30 (0.98-5.42)		0.81 (0.09-7.08)	
Pathologic tumor size (cm)	1.10 (0.82-1.46)	.538	0.39 (0.11-1.43)	.155
Neoadjuvant chemotherapy		.624		.390
No	Reference		Reference	
Yes	0.84 (0.42-1.70)		2.57 (0.30-22.07)	
Adjuvant chemotherapy		.183		
No	Reference		Reference	
Yes	2.25 (0.68-7.42)		NR	
CTV volume (cc)	1.02 (0.98-1.05)	.414	1.01 (0.94-1.08)	.760
PTV volume (cc)	1.01 (0.98-1.04)	.414	1.03 (0.97-1.09)	.334
PTV V100% (%)	1.01 (0.97-1.05)	.565	1.04 (0.92-1.16)	.589
BED_{10}	1.00 (0.96-1.06)	.760	1.17 (0.72-1.92)	.562
$EQD2_{10}$	1.01 (0.95-1.07)	.760	NR	.818

Abbreviations: BED_{10} = biologically effective dose using an alpha/beta ratio of 10; CI = confidence interval; CTV = clinical target volume; $EQD2_{10}$ = equivalent dose in 2 Gray per fraction using an alpha/beta ratio of 10; HR = hazard ratio; LF = local failure; NR = not reportable; PTV = planning target volume; PTV V100% = percent of PTV that received 100% of the prescription dose.

failures in between the diaphragm and bottom of L3, while Kharofa et al considered LFs as failures within the SBRT volume or within institutional fractionated volumes that electively covered the regional vasculature. In our analysis, because no elective nodal volumes were treated, we constrained the definition of LF to failures within the operative bed based on preoperative tumor location to minimize inclusion of nodal failures. Despite this constrained definition, LFs were identified in 42.1% of patients after SBRT targeted to close/positive margins. Thus, true LFs occur in a significant proportion of patients, despite SBRT targeting the areas of highest risk of recurrence. Of 72 patients with available imaging and SBRT plans, only 6 (8.3%) experienced an LF within the treatment volume; the majority of LFs were outside or marginal to the treatment volume. This suggests issues

with volume and not dose, and thus expanding treatment volumes to include all portions of the pancreas/pancreatic bed and abutting vasculature may be warranted. Because RTOG consensus volumes encompassed most LFs as well as RFs in this study, adopting a similar philosophy with SBRT treatment volumes may be warranted if feasible.

We note several limitations of this study, including its retrospective nature, relatively small sample size, and the subjective nature of mapping LFs and RFs to PTV volumes and RTOG consensus volumes. The latter issue was mitigated by systematically noting the location and distance of failures relative to abdominal vasculature, which allowed for more precise mapping.

Conclusions

In patients with resectable or borderline resectable adenocarcinoma of the pancreas who received adjuvant SBRT for close or positive margins, the majority of LFs occurred outside the PTV. Future trials involving adjuvant SBRT or hypofractionated RT should consider expansion of treatment volumes if feasible.

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